

### REMARKS

Claims 1 to 25 are pending. Claim 25 stands withdrawn from consideration. Claim 1 is currently amended.

Support for the clarifying amendment to claim 1 may be found, for example, in the specification on page 8, lines 6-8 and on page 11, lines 7-10.

Reconsideration of the application is requested.

### § 112 Rejections

**Claims 1-24 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

The Patent Office argues that there is insufficient antecedent basis in Claim 1 for the recited limitation "the excipient package" in lines 13-14 of the claim.

In response, Applicants submit that the current amendment to claim 1 overcomes the rejection of claims 1-24 under 35 USC § 112, second paragraph, and that the rejection should be withdrawn.

### § 103 Rejections

**Claims 1-5, 8, and 10-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. [Journal of Pharmaceutical Sciences, 1965, volume 54, pages 591-594, hereinafter "Katz et al."] in view of Tayar et al. [Journal of Pharmaceutical Science, volume 80, 1991, pages 590-598, hereinafter "Tayar et al."] in view of Loftsson et al. [Drug Development and Industrial Pharmacy, 1994, volume 20, pages 1699-1708, hereinafter "Loftsson et al. (1994)"] in view of Loftsson et al. [Drug Development and Industrial Pharmacy, 1997; volume 23, pages 473-481, hereinafter "Loftsson et al. (1997)"] in view of Lipinski et al. [Advanced Drug Delivery Reviews, volume 23, 1997, pages 3-25, hereinafter "Lipinski et al."].**

The Patent Office asserts that Katz et al. teach, in Table 1, molecular weights and partition coefficients for a plurality of molecules. The Patent Office argues that molecular

weights are deduced from the columns listing the combination of weight by volume concentrations and the molar concentrations, while partition coefficients are listed in the fifth column of data. The Patent Office submits that compounds listed in Table 1 are of the cortisone family, and applies hydrocortisone as the model compound and applies dexamethasone as the pharmaceutical.

The Patent Office argues that Table 1 of Katz et al. compares the properties of hydrocortisone, dexamethasone and other related compounds, particularly with respect to size (in the form of molecular weight) and hydrophobicities (in the form of partition coefficients). The Patent Office further argues that McKenzie parameter ( $p_{McK-S_{50}}$ )s are calculated in the last column as the negative logarithm of dilution producing vasoconstriction of 50% of subjects, while the partition coefficients are experimentally measured. The Patent Office further argues in essence that Katz et al. disclose that prepared dilutions of the corticosteroids in various dilutions were applied to areas of the forearm and covered with Saran wrap, thereby meeting the requirements of skin of a live mammal are met. The Patent Office further argues that Saran wrap comprises an adhesive patch, and the chemical is in contact with the adhesive patch (the Saran wrap) before it penetrates the skin, and that the entire system comprises a transdermal delivery system.

The Patent Office admits that Katz et al. fail to teach:

- (1) the compound-excipient formulation, the diffusion method and analysis, saturation of the model compound, impact of rotatable and hydrogen bond donors and acceptors, use of a Franz cell(s), a plurality of excipients, utilization of a chemical reaction, use of a synthetic polymer membrane, calculated and empirical parameters of the pharmaceutical, and a transdermal delivery system;
- (2) the partition coefficient between octanol and water; and
- (3) choosing a model and a pharmaceutical, which are different compounds, based on size (molecular weight) and partitioning.

Regarding item 1, the Patent Office argues that Loftsson et al. (1994) teach a method of making a pharmaceutical composition between hydrocortisone and different cyclodextrins to enhance transdermal delivery, and refers to Figure 2 of Loftsson et al. (1994). The Patent Office

further argues that the HPPCD- hydrocortisone complex in Loftsson et al. (1994) is chosen because of their compatibilities in size (i.e., the molecular weight of the hydrocortisone allows the molecule to fit into the cyclodextrin) and partitioning (i.e., the cyclodextrin is enabled to partition hydrophobically into the molecule). The Patent Office further argues that hydrocortisone is able to transdermally penetrate the body with the aid of the cyclodextrin excipient.

Regarding item 2, the Patent Office argues that Tayar et al. teach the solvation of solutes in different solvent systems, including an octanol-water solvent system, to tune for a desired comparison of aqueous solvability to lipophilicities.

The Patent Office submits that Loftsson et al. (1994) teach use of Franz diffusion cells to measure diffusion across hairless mouse skin. The Patent Office further submits that Loftsson et al. (1994) teach that the chemical reaction between the cyclodextrin and the hydrocortisone is used to affect the diffusion across the skin. The Patent Office further submits that Loftsson et al. (1994) teach that the formulation is chosen from one of two different cyclodextrins employed throughout the study. The Patent Office argues that in Loftsson et al. (1994) the standard deviation of the flux is calculated while the flux is an experimentally measured property.

The Patent Office admits that Katz et al, Tayar et al., Loftsson et al. (1994) do not teach choosing a model and a pharmaceutical, which are different compounds, based on size (molecular weight) and partitioning. The Patent Office asserts that Loftsson et al. (1997) teach the use of the pharmaceutical. The Patent Office argues in essence that Loftsson et al. (1997) teach that cyclodextrins are pharmaceutical excipients. The Patent Office further argues that Loftsson et al. (1997) diagrams the structure of dexamethasone on which a number of rotatable bonds and hydrogen bond donors and acceptors are illustrated, and that the HPPCD-dexamethasone complex is chosen because of the compatibilities in size (allowing the molecule to fit into the cyclodextrin) and partitioning (enabling the dexamethasone to partition hydrophobically into the cyclodextrin).

The Patent Office admits that Katz et al. Tayar et al., Loftsson et al. (1994), and Loftsson et al. (1997) do not teach choosing a model and a pharmaceutical based on size (molecular weight) and partitioning.

The Patent Office applies Lipinski et al. for their discussion of characteristics (including molecular weight and log P) that are used as estimates to select or design potential drugs.

The Patent Office argues in essence that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to modify the general corticosteroid study of Katz et al. by use of the cyclodextrin combination with hydrocortisone (the model compound) of Loftsson et al. (1994) by use of the cyclodextrin combination with dexamethasone of Loftsson et al. (1997) by use of the five system partition (including octanol-water) study of Tayar et al., and by use of molecular weight and log P as in Lipinski et al., because while Katz et al. tabulate the relevant molecular weights and partition coefficients of the compounds of interest, Loftsson et al. (1994) teach the formulation of the model compound-excipient complex for the purpose of understanding transdermal transport phenomena, Loftsson et al. (1997) teach the formulation of the pharmaceutical-excipient complex for the purpose of ameliorating eye disease, and Lipinski et al. teach the significance of molecular weight and partition coefficients in the design and selection of drugs. The Patent Office further argues that it would be obvious to adjust the partition study of Katz et al. from water-ether to water-octanol according to the procedures of the study of Tayar et al. for a desired comparison of aqueous solvability with lipophilicities. In support, the Patent Office argues that the two types of partition coefficients are art accepted equivalents.

In response, and without conceding the Patent Office's characterization of the cited references or admitting that the rejection is even proper, it is submitted that a central theme to Applicants' invention is the choice and use of model compound(s) in place of pharmaceutical(s) in the development of excipient packages for use with the pharmaceutical(s), for example, in a further, refined testing regimen. For example, currently amended claim 1 broadly claims (emphasis added):

A method of formulating a pharmaceutical composition comprising:  
**comparing** parameters of at least one pharmaceutical and a plurality of compounds, wherein the parameters consist of at least log(P) and molecular weight;  
based on the compared parameters, **choosing** at least one model compound from the plurality of compounds for each pharmaceutical, wherein the at least one model compound is different from the at least one pharmaceutical;

**providing** at least one model compound-excipient formulation comprising at least one model compound and at least one excipient;  
**measuring** the diffusion of a model compound of at least one model compound-excipient formulation across at least one membrane;  
**choosing** a model compound-excipient formulation based on the measured model compound diffusion; and  
**combining** components comprising the at least one pharmaceutical and the at least one excipient of the chosen model compound-excipient formulation."

Notwithstanding the arguments made by the Patent Office in the instant rejection, it is respectfully submitted that the cited references neither teach nor properly suggest this central feature of using a model compound in place of a pharmaceutical during formulation of a pharmaceutical-excipient formulation as in the instant invention, much less using parameters consisting of at least log(P) and molecular weight.

For example, it is submitted that while Katz et al. may compare various properties of hydrocortisone, dexamethasone, and other related compounds, and how they influence percutaneous absorption (e.g., see Katz et al. in the Abstract and the Conclusion) it does not teach or properly suggest using a model compound in place of a pharmaceutical during formulation of a pharmaceutical-excipient formulation as in the instant invention as in set forth in current claim 1.

Similarly, it is submitted that while Loftsson et al. (1994) may report the ability of cyclodextrins, optionally in combination with water-soluble polymers, to affect topical drug delivery to the eye (e.g., see Loftsson et al. (1994) in the Abstract and the Conclusions), it does not teach or properly suggest using a model compound in place of a pharmaceutical during formulation of a pharmaceutical-excipient formulation as in the instant invention as in set forth in current claim 1.

Likewise, it is submitted that while Tayar et al. may report influences of hydrogen bonding capacity and polarity on partitioning of solutes in octanol-water (e.g., see Tayar et al. in the Abstract), it does not teach or properly suggest using a model compound in place of a pharmaceutical during formulation of a pharmaceutical-excipient formulation as in the instant invention as in set forth in current claim 1.

Moreover, it is also submitted that while Loftsson et al. (1997) may report the use of hydrocortisone as a sample drug (e.g., see Loftsson et al. (1997) on page 1700, last paragraph) to study the effect of HPBCD on the release of drugs from topical vehicle systems, at most they only report general effects of HPBCD to keep drug molecules in solution during transdermal delivery, and do not teach or properly suggest the amounts to use if using such drugs. Clearly, they do not teach or properly suggest using a model compound in place of a pharmaceutical during formulation of a pharmaceutical-excipient formulation as in the instant invention as in set forth in current claim 1.

Finally, it is submitted that while Lipinski et al. may report characteristics (including molecular weight and log P) that are used as estimates to select candidates for further screening as potential drugs, the major thrust of Lipinski et al. is directed to calculation or measurement of solubility properties of the actual drug candidates themselves (e.g., see Lipinski et al. in the Abstract) not model compounds. Nor are Lipinski et al. particularly directed at the problem of excipient formulation. Clearly, they do not teach or properly suggest using a model compound in place of a pharmaceutical during formulation of a pharmaceutical-excipient formulation as in the instant invention as in set forth in current claim 1.

Regarding several further points, with regard to the Patent Office's argument that molecular weights are deduced in Katz et al., it is submitted that there is no evidence in Katz et al. that this was literally done or even appreciated. Further, regarding the Patent Office's characterization of Loftsson et al. (1997), it is submitted that size does not necessarily determine molecular weight (e.g., factors such as geometric constraints and the presence of heavy atoms (e.g., S, Cl, Br) and the like each can play significant roles). Moreover, it is submitted that Fig. 2 of Loftsson et al. would in no way teach or properly suggest to one of ordinary skill in the art to look at the number of rotatable bonds in the model compound.

In view of the foregoing discussion, it is respectfully submitted that none of the applied references teach or properly suggest using a model compound in place of a pharmaceutical during formulation of a pharmaceutical-excipient formulation as in the instant invention as in set forth in claim 1. Moreover, it is not credible that one of ordinary skill in the art in possession of these references at the time the instant invention was made could, much less would, even be able to arrive at the claimed invention. Rather, it is submitted that the Patent Office's attempt, which

seems unclear, necessarily relies on hindsight reasoning basely solely on Applicants own disclosure.

For at least these reasons, it is submitted that the rejection of claim 1 under 35 USC § 103(a) as being unpatentable over Katz et al. in view of Tayar et al. in view of Loftsson et al. (1994) in view of Loftsson et al. (1997) in view of Lipinski et al. has been overcome and should be withdrawn. Claims 2-5, 8, and 10-24 each add additional features to patentable claim 1, and are hence likewise patentable.

In summary, the rejection of claims 1-5, 8, and 10-24 under 35 USC § 103(a) as being unpatentable over the combination of Katz et al. in view of Tayar et al. in view of Loftsson et al. (1994) in view of Loftsson et al. 1997 in view of Lipinski et al. has been overcome and should be withdrawn.

**Claims 1 and 6-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al., in view of Tayar et al., in view of Loftsson et al. (1994), in view of Loftsson et al. (1997), in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al. [Chemistry- A European Journal, 1999, volume 5, pp. 897-901, hereinafter "Garcia-Ochoa et al."].**

The Patent Office admits that Katz et al. in view of Tayar et al. in view of Loftsson et al. (1994) in view of Loftsson et al. (1997) in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above fails to disclose any use of fluorescence or fluorescence spectroscopy.

The Patent Office submits that Garcia-Ochoa et al. teaches detecting cyclodextrins with fluorescent dyes for better visualization of excited-state intramolecular proton transfer (ESIPT) reactions.

The Patent Office argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz et al., in view of Tayar et al., in view of Loftsson et al. (1994), in view of Loftsson et al. (1997), in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al., for Garcia-Ochoa et al. is an extension of the cyclodextrin study with the use of fluorescence to more effectively monitor cyclodextrin concentration and location for purposes such as monitoring of ESIPT reactions.

In response, it is submitted that Garcia-Ochoa et al. fail to overcome the deficiencies of Katz et al., in view of Tayar et al., in view of Loftsson et al. (1994), in view of Loftsson et al. (1997), in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 as discussed above.

Hence, the combination of Katz et al., in view of Tayar et al., in view of Loftsson et al. (1994), in view of Loftsson et al. (1997), in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al. fails to teach or properly suggest the method of claim 1, which is patentable. Claims 6 and 7 each add additional features to patentable claim 1, and are hence likewise patentable.

In summary, the rejection of claims 1 and 6-7 under 35 USC § 103(a) as being unpatentable over the combination of combination of Katz et al., in view of Tayar et al., in view of Loftsson et al. (1994), in view of Loftsson et al. (1997), in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al. has been overcome and should be withdrawn.

**Claims 1 and 8-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Tayar et al. in view of Loftsson et al. (1994) in view of Loftsson et al. (1997) in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Colarusso et al. [Biophysical Journal; February 2002; volume 82, pages 752-761, hereinafter "Colarusso et al."].**

The Patent Office admits that Katz et al. in view of Tayar et al. in view of Loftsson et al. (1994) in view of Loftsson et al. (1997) in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, fail to record any images in their studies.

The Patent Office submits that the article of Colarusso et al. reveals MDCK cell apical membrane topography and uses fluorescence and microscopy imaging techniques for a more clear visualization of apical membrane features. The Patent Office further submits that Colarusso et al. illustrate several fluorescent images of cells and the effects of cyclodextrins on them in Figures 1-4 and 6-7.

The Patent Office argues it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz et al. in view of Tayar et al. in view of

Lofsson et al. (1994) in view of Lofsson et al. (1997) in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Colarusso et al. because Colarusso et al. use cyclodextrins and fluorescence in analyzing images of cells for a more clear illustration of cellular processes.

In response, it is submitted that Colarusso et al. fail to overcome the deficiencies of Katz et al. in view of Tayar et al. in view of Lofsson et al. (1994) in view of Lofsson et al. (1997) in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above.

Hence, the combination of Katz et al., in view of Tayar et al., in view of Lofsson et al. (1994), in view of Lofsson et al. (1997), in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Colarusso et al. fails to teach or properly suggest the method of claim 1, which is patentable. Claims 8 and 9 each add additional features to patentable claim 1, and are hence likewise patentable.

In summary, the rejection of claims 1 and 8-9 under 35 USC § 103(a) as being unpatentable over the combination of combination of Katz et al., in view of Tayar et al., in view of Lofsson et al. (1994), in view of Lofsson et al. (1997), in view of Lipinski et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Colarusso et al. has been overcome and should be withdrawn.

In view of the above, it is submitted that the application is in condition for allowance. Examination and reconsideration of the application as amended is requested.

Respectfully submitted,

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